Prediction of Peptide Conformation: The Adaptive Simulated Annealing Approach

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ABSTRACT

We report the application of the adaptive simulated annealing (ASA) method as a global optimization approach to biomolecular structure determination, using the ECEPP/2 (empirical conformation energy program for peptides) potential energy form. As applied to Met-enkephalin, our optimization results in a conformation that is in agreement with other studies. In addition, a dominant right-handed α-helical conformation is predicted for a 14-residue poly (L-alanine) model peptide in a limited search range. These results show that ASA is an efficient and robust algorithm for conformational analysis. © 1997 by John Wiley & Sons, Inc.

Introduction

Biopolymers of defined secondary and tertiary structure derivatized with chromophores may be well suited for use as nonlinear optical materials.[1–5] Polypeptides provide the flexibility of controlling backbone structure, thereby providing temporal stability to attached chromophores. Although it is of importance to understand the effects of the chromophore, molecular dynamics calculations explain only local effects.[4] Indeed, the design of chromophore-based biomaterials requires the development of techniques to determine a priori the molecular structure of such systems. To define a preliminary folding pattern of larger biomolecules, an integrated computational tool can be utilized,[6] in which a neural network trained on the Protein Data Base is applied to predict the spatial proximity of amino acid residues that are less than a given threshold apart,[7] and the double-iterated Kalman filter technique[8] is then employed to determine the structural motifs at a low resolution.[9] However, such approaches cannot be applied to peptide-bound chromophores, and moreover, the structures thus predicted have to be further refined by energy minimization, for which robust and efficient algorithms are necessary.

For systematic or grid searches of global minima the number of points in configuration space increases exponentially with the number of variables, rendering these methods impractical for large molecules, although some promising efforts

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have been recently reported using a parallel direct search.[10] A variety of approaches have been developed to reduce the scope of conformational search, specifically by imposing constraints, or biasing the search toward regions where the lowest energy may lie. These stochastic and deterministic methods have been recently reviewed,[11–13] where the former include simulated annealing (SA),[14–18] Monte Carlo (MC) with minimization (MCM),[19–20] Monte Carlo biased with Ramachandran's plot,[21] the multicanonical ensemble[22] and random cost approaches,[23] and genetic algorithms (GA),[24,25] whereas the latter include molecular dynamics with minimization,[26] the diffusion equation method,[27] the mean field technique,[28] and dynamic programming,[29] all of which differ markedly in effectiveness. Nevertheless, these methods are still limited by the high dimensionality of the problem and low efficiency. It is therefore of importance to further develop efficient algorithms for conformational analysis.

The recently developed ASA algorithm[30] has been shown to be faster and more efficient than Boltzmann annealing, and possibly more efficient even than GAs.[31] In this article we report the application of the ASA approach to biomolecular structure determination, specifically for Met-enkephalin and a model poly(L-alanine) system. We outline some of the aspects of the method, the form of the potential energy used, and specific computational details. The reported results prove the algorithm to be robust and efficient for conformational search applications.

Methods

ADAPTIVE SIMULATED ANNEALING

Within conventional simulated annealing[14] the cooling schedule is given by:

$$T_k = T_0 e^{-(1-c)k}, \quad (0 < c < 1) \tag{2.1}$$

where trial and error are applied to determine the annealing rate, $c - 1$, as well as the starting temperature, T_0. A MC simulation is carried out at each temperature step k with temperature T_k. This cooling schedule is equivalent to $T_{k+1} = T_k c$. Modifications previously suggested[16,19] include moving a number of dihedral angles in a MC step; adjusting the maximum deviation of the variables as the temperature decreases to ensure that the acceptance ratio is more than 25%; and treating the variables differently according to their importance in the folding process, for instance, by increasing sampling for the backbone dihedral angles as compared to those of the side-chains. It is interesting to point out that, within ASA, these modifications are implicitly included.

Details of the ASA algorithm are described elsewhere (ref. 30 and references therein), with only the pertinent aspects of the method being summarized in this discussion. We consider a system described by a cost function, $E(\{p^i\})$, where p^is values ($i = 1, 2, 3, \ldots D$) are parameters (variables) having ranges $[A_i, B_i]$.

MC Configurations.

As the kth point is saved in a D-dimensional configuration space, the new point, p^i_{k+1}, is generated by:

$$p^i_{k+1} = p^i_k + y^i(B_i - A_i) \tag{2.2}$$

where the random variables y^i in $[-1, 1]$ (nonuniform) are generated from a random number u^i uniformly distributed in [0, 1], and the temperature T_i associated with parameter p^i, as follows:

$$y^i = \mathrm{sgn}(u^i - 0.5)T_i\left[(1 + 1/T_i)^{|2u^i - 1|} - 1\right] \tag{2.3}$$

Note that if p^i_{k+1} is outside the range of $[A_i, B_i]$ it will be disregarded, with the process being repeated until it falls within the range. The choice of y^i is made so that the distribution of each parameter, given by the distribution function:

$$g^i(y^i; T_i) = 1/\left[2(|y^i| + T_i)(1 + 1/T_i)\right] \tag{2.4}$$

is chosen to ensure that any point in configuration space can be sampled infinitely often in annealing time with a cooling schedule outlined below (cf. eq. (14) in ref. 30). Thus, at any annealing time k_0, the probability of not generating a global optimum, given infinite time, is zero:

$$\prod_{k=k_0}^{\infty}(1 - g_k) = 0 \tag{2.5}$$

where g_k is the distribution function at time step k. Note that all atoms move at each MC step in ASA. A Boltzmann acceptance criterion is then applied to the difference in the cost function.

Annealing Schedule

The annealing schedule for each parameter temperature from a starting temperature, T_{0i}, and similarly for the cost temperature, is given by:

$$T_i(k_i) = T_{0i}\exp(-c_i k_i^{1/D}) \tag{2.6}$$

where c_i and k_i are the annealing scale and ASA step of parameter p^i.

Reannealing

The temperatures may be periodically reannealed or rescaled according to the sensitivity of the cost function. At any given annealing time, the temperature range is ''stretched out'' over the relatively insensitive parameters, thus guiding the search ''fairly'' among the parameters. The sensitivity of the energy to each parameter is calculated by:

$$S_i = \frac{\partial E}{\partial p^i} \tag{2.7}$$

while the reannealing temperature is determined by:

$$T_i(k') = T_i(k)\frac{S_i}{S_{\max}} \tag{2.8}$$

In this way, less sensitive parameters anneal faster, Note that since the initial acceptance temperature is set equal to a trial value of the cost function, this is typically very large relative to the global minimum. Therefore, when this rescaling is performed, the initial acceptance temperature is reset to the most current minimum of the cost function, and the annealing time associated with this temperature is set to give a new temperature equal to the lowest value of the cost function encountered to annealing date. The index of annealing and reannealing of the cost function is determined by the number of accepted points instead of the number of generated points as used for the parameters. This is done approximately every 100 accepted events.

The ASA algorithm is mostly suited to problems for which less is known about the system, and has proven to be more robust than other simulated annealing techniques for complex problems with multiple local minima; for example, as compared to Cauchy annealing where $T_i = T_0/k$, and Boltzmann annealing where $T_i = T_0/\ln k$. The annealing schedule in eq. (2.1), faster than ASA for a large dimension of D, does not pass the infinitely often annealing-time test in Eq. (2.5), and is therefore referred to as simulated quench in the terminology of ASA.

POTENTIAL ENERGY

Within ECEPP[32,33] bond lengths and bond angles are kept constant, and the dihedral angles are being varied. It is given in the form:

$$U = E_{nb} + E_{es} + E_{tor} \tag{2.9}$$

where E_{nb}, E_{es}, and E_{tor} are nonbonded (Lennard–Jones and hydrogen-bonding), electrostatic, and torsional energies, respectively, expressed as:

$$E_{nb} = \sum_{i\neq j}\epsilon_{ij}\left[F\left(\frac{r_{ij}^0}{r_{ij}}\right)^{12} - 2\left(\frac{r_{ij}^0}{r_{ij}}\right)^{6}\right] \tag{2.10}$$

$$+ \sum_{i'\neq j'}\epsilon_{ij}\left[5\left(\frac{r_{ij}^0}{r_{ij}}\right)^{12} - 6\left(\frac{r_{ij}^0}{r_{ij}}\right)^{10}\right] \tag{2.11}$$

$$E_{es} = \sum_{i\neq j}\frac{q_i q_j}{D r_{ij}} \tag{2.12}$$

$$E_{tor} = \sum_k \frac{A_k}{2}(1 \pm \cos n\theta_k) \tag{2.13}$$

where ϵ_{ij} and r_{ij}^0 are the potential depth and the position of the minimum of the 12–6 or 12–10 pair potentials; q is the partial atomic charge; A_k is the barrier height of rotation around the kth bond; θ_k is the dihedral angle; n is the n-fold degeneracy of the torsional potential; and F is assigned the value 0.5 for interactions between atoms three bonds apart or the value 1 otherwise. The 12–10 potential models hydrogen bonds.

Computational Details

The Met-enkephalin model was constructed as (H-Tyr-Gly-Gly-Phe-Met-OH). For the 14 (L-alanine) model, the neutral NH_2— and —COOH end groups were substituted at the termini, as is

also reported in ref. 21, whereas in other studies[20] the backbone is terminated by the ($COCH_3$) group at the amino end, and ($HNCH_3$) at the carboxyl end. Note that the backbone was found to fold faster when the NH_2— and —COOH blocking groups were utilized.

We integrated the ASA code (in C) with the ECEPP/2 potential form (in FORTRAN), and the computations were performed on a SGI IRIS 4D/420VGX. Each ASA run was started from random initial configurations, namely, random (ϕ, ψ) backbone and (χ) side-chain dihedral angles. The initial temperature was determined by the average energy of five or ten random samplings, and a full search of the dihedral angles ($-\pi$, π) was set. The dihedral angle, ω, was fixed to 180° in all of the ASA runs. The typical maximum number of calls to the energy function was 30,000 (with about 60 function calls for each second cpu time). An ASA was terminated if it repeated the best energy value for three or five reannealing cycles (each cycle generates 100 configurations). Further refinement of the final ASA-optimized configuration was carried out by using the local minimizer SUMSL,[35] or the conjugate gradient method. The combination of the ASA application and a local minimizer improved the efficiency of the search.

The ASA calculation is governed by various control parameters,[30] for which the most important setting is the annealing rate for the temperatures of ''cost'' and ''parameters,'' determined by the so-called ''temperature ratio scale'' (the ratio of the final to the initial temperature after certain annealing steps) and the ''cost parameter scale.'' Note that the ''cost'' within the ASA nomenclature is the potential energy, whereas a ''parameter'' is a dihedral angle variable. The control parameters were varied to improve the search efficiency. Adequate control parameters used for obtaining the results reported in this study were: ''temperature ratio scale'' = 10^{-4} and ''cost parameter scale'' = 0.5. These parameter settings correspond to an annealing rate for the energy of $c_{cost} = 3.6$, and for the dihedral angles of $c_{parameter} = 7.2$. Note that the annealing rate for all dihedral angles was chosen to be the same.

Results and Discussion

The ASA algorithm was applied to the structure determination of Met-enkephalin, with the dihedral angles ω fixed (to 180°), thus totalling in 19 variables. This molecule has a complicated energy surface.[16,18] In previous studies of Met-enkephalin using the ECEPP force field,[19] the less efficient MCM approach was applied, where a local minimization was carried out after each generated random configuration. The lowest energy for Met-enkephalin was found to be −12.9 kcal/mol using the 1984 version of ECEPP/2[20] (−1.60 kcal/mol with the 1983 version of ECEPP/2). Furthermore, in a SA application,[16] only conformations with energies of −2.2 kcal/mol (instead of −12.9 kcal/mol) were identified. In these reports, the dihedral angles ω were not fixed, whereas for studies where ω values were fixed, the lowest energy was found to be −10.7 kcal/mol by MCM[36] (unpublished). Similar geometries (with ω values fixed) were reported when applying SA[17] and the multicanonical algorithm.[22] The ECEPP/2 energies that were obtained in those studies[17,22] were somewhat different: the lowest energy reported (−12.1 kcal/mol) is only −9.9 kcal/mol when using a local minimization with the original ECEPP/2 code, and assumes the value of −10.7 kcal/mol only after a change of the first dihedral angle of TYR from 98° to −87°.

Using different initial conformations and control parameter settings of the cooling schedule, 55 independent ASA runs were carried out. Table I summarizes the energy distribution of these calculations. Most of the ASA calculations result in energies in the range of −8 to −3 kcal/mol, with seven of the results determining conformations having energies that are only 3 kcal/mol above the known lowest energy, thus exhibiting the effectiveness of the approach. Moreover, as the range of search was somewhat narrowed, almost all of the ASA runs reach the global energy minimum. Preliminary results using the 1983 version of ECEPP/2 have been published elsewhere.[37]

Indeed, for the full range search, we identified three conformations with energies of −10.6, −10.4,

TABLE I.
The Energy (E, kcal / mol) Distribution of ASA Runs for Met-Enkephalin Using a Full Search Range.

	$E < -8$	$-8 < E < -5$	$-5 < E < -3$	$E > -3$
No. of ASA runs	7	19	19	10

TABLE II.
Energy (E, kcal / mol) and Dihedral Angles of Lowest Energy Conformations of Met-Enkephalin Obtained by ASA Optimizations. A0 and A Are Lowest-Energy Conformations Obtained by MCM with ω Nonfixed and Fixed, Respectively (Taken from Refs. 16 and 36).

	Conformation						
	A0	A	1	2	3	4	5
	$E = -12.9$	$E = -10.7$	$E = -10.6$	$E = -10.4$	$E = -10.1$	$E = -8.5$	$E = -8.7$
ϕ_1	−86	−87	−87	−87	−87	−87	−87
ψ_1	156	154	153	153	156	153	154
ϕ_2	−155	−162	−161	−162	−166	−166	−167
ψ_2	84	71	72	75	87	72	73
ϕ_3	84	64	64	63	68	63	76
ψ_3	−74	−93	−94	−95	−91	−97	−77
ϕ_4	−137	−82	−83	−81	−103	−74	−93
ψ_4	19	−29	−26	−30	−13	−30	−42
ϕ_5	−164	−81	−79	−76	−76	−82	−164
ψ_5	160	144	133	132	137	143	−13
χ_1^1	−173	−180	180	179	−166	−180	177
χ_1^2	79	−111	−110	71	88	73	−115
χ_1^3	−166	145	145	−35	−148	−179	156
χ_4^1	59	180	72	−179	71	179	178
χ_4^2	−86	−100(80)	84	−100	−93	−100	54
χ_5^1	53	−65	−171	−173	−65	−65	64
χ_5^2	175	−179	176	176	−178	−179	−172
χ_5^3	−180	−179	180	179	−178	−179	−180
χ_5^4	−58	−180(−60)	−60	60	−178	−179	−180
Backbone rms (Å)	0	0.04	0.07	0.51	0.26	0.91	
All-atom rms (Å)	0	2.52	1.92	2.08	1.29	2.03	

and −10.1 kcal/mol, that exhibit the configuration of the known lowest geometry of −10.7 kcal/mol. In this search the backbone ω dihedral angles were fixed to enable direct comparisons with more of the available studies, hence confirming the efficiency of the ASA algorithm. Table II lists the conformations of these lowest energy configurations, as well as additional low energy structures. The first two conformations, #1 and #2, have almost the same backbone configuration as that of A (−10.7 kcal/mol), with a backbone root-mean-square (rms) deviation of only 0.04 and 0.07 Å, respectively. The all-atom rms of all the listed conformations with energies ranging from −8.5 to -10.6 kcal/mol are about 2 Å. For conformations #1 and #2, the noted differences are in the side-chains, corresponding to a 0.1- and 0.3-kcal/mol difference in energy, respectively. Note that if we change the dihedral angles ω to 180° for the geometry of energy −12.9 kcal/mol reported in ref. 20, its nearest local minimum reached is one with energy −9.7 kcal/mol, rather than the ''global minimum'' of energy −10.7 kcal/mol, indicating that fixing ω does affect the location of the global energy minimum, although it is not a very significant difference. For a comparison with the study reported in ref. 16, we also carried out a series of calculations in which ω values were not fixed (24 variables), resulting in the lowest energy of −9.3 kcal/mol (about 50% of the runs resulted in energies lower than −5.5 kcal/mol).

The ASA algorithm was applied to a model of (L-alanine), which is known to assume a dominant right-handed α-helical structure.[20, 34] For a search range of dihedral angles that includes both the right-handed (RH) α-helix and the β-sheet region in the Ramachandran diagram, ψ:(−115, −180) and ϕ:(−115, 0), it was significant to find RH α-helices with $\phi \approx -68°$ and $\psi \approx -38°$ in all backbones except those near the end groups, as shown in Table III. The energy of such a geometry is typically −10.2 kcal/mol after a local minimization. The energy surfaces of the RH α-helical regions were found to be less complex than those of

TABLE III.
The Final Conformation of a Model 14 (L-Alanine) Peptide Calculated by ASA.[a]

	2	3	4	5	6	7	8	9	10	11	12	13	14	15
ϕ	−99.4	−68.2	−68.0	−69.3	−66.9	−68.3	−66.7	−68.8	−67.1	−69.4	−65.0	−67.2	−87.7	−75.9
ψ	158.1	−34.3	−38.8	−38.5	−38.6	−39.2	−38.0	−38.7	−37.7	−39.6	−40.0	−44.6	−65.8	−40.1

[a]The constraints are: $\phi(-115, 0)$, $\psi(-115, 180)$, $\omega = 180°$, and $\chi_1 = 61.5°$. The total energy is −9.1 kcal / mol (CG minimization of a right-handed α-helix yields an energy of −10.2 kcal / mol), with $\phi \approx -68°$, $\psi \approx -38°$).

Met-enkephalin. These results are consistent with a previous study.[18]

Conclusions

The application of adaptive simulated annealing as a global optimization method for structure determination of biomolecules, has shown that the ASA algorithm is efficient and robust for conformational analysis, as compared to conventional simulated annealing techniques. In particular, it is comparable to the SA study reported in ref. 20, while showing a better performance than the one reported in ref. 16. As applied to Met-enkephalin, our optimization results in a conformation with an energy of −10.6 kcal/mol (applying the ECEPP/2(1984) potential), which is similar to the previously reported value (−10.7 kcal/mol). Utilizing a partial search range improves the efficiency significantly, showing that ASA may also be useful for refinement of a molecular structure predicted or measured by other methods. A dominant right-handed α-helical conformation was found for the 14-residue (L-alanine) model, with deviations observed only near the end groups. Simulation efficiency could be further improved by adopting parallelization, particularly by performing multiple minimizations concurrently from different starting configurations, and evaluating functions and their derivatives in parallel at different atoms. Preliminary attempts were recently reported for simulated annealing.[39]

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